Phenmetrazine Hydrochloride

A Clinical Evaluation of a New Anoretic Agent

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• **Phenmetrazine hydrochloride appeared to be a safe anoretic agent and was effective in weight control in 80 per cent of a series of 49 obese patients.**

Tolerance to the drug did not develop in periods up to 18 weeks of continued treatment.

Phenmetrazine was most effective in patients under 45 years of age in this series.

Side effects were minimal and easily controlled. No allergic or toxic effects were noted.

A NEW ANORETIC AGENT, phenmetrazine hydrochloride (Preludin®*), has had extensive use in Europe, especially in Germany, over the past two years with encouraging results.[2,4,7] A number of clinical reports have recently appeared in this country as well.[3,5,6]

Phenmetrazine has the chemical formula of 2-phenyl-3 methyl-tetrahydro-1, 4 oxazine hydrochloride and is a white, odorless, crystalline powder with a bitter taste. The toxicity of the drug, as judged both by the LD_{50} in mice and the amount needed for central nervous system excitement, is approximately one-fifth that of amphetamine.[8] Phenmetrazine in the same dose as epinephrine has a relatively weak effect on blood pressure; in dogs it brings about approximately one one-thousandth as much rise in blood pressure.[8] The mode of the anoretic action of this drug has not yet been determined.

Results of a clinical evaluation of its effect on obesity are presented in this communication.

MATERIAL AND METHODS

The subjects of this study were an unselected group of persons who attended the Obesity Clinic which had been established for the sole purpose of studying the problem of obesity. The majority of these patients had been observed carefully for a number of years in the clinic and had shown only slight reduction of weight on previous dietary and drug regimens. Forty-nine patients were included in this study. All but one were females. The average age was 47, with a range of 15 to 73 years. The average weight at the beginning of the study was 208.3 pounds and the range was 132 to 346 pounds.

No specific dietary restrictions were employed during the period of this study except that patients who were already following dietary regimens were advised at the beginning of the study to make no changes. No other anoretic agents were used, but previous therapy such as administration of diuretics, desiccated thyroid and sedatives was not discontinued. All the patients had been observed for long periods during which their weight had fluctuated little.

A technique using identical appearing tablets was employed. These were labeled A66 and B66, and the investigators were not told which tablet contained the active drug. Each bottle was marked as containing 25 mg. tablets. Each patient took one tablet 30 minutes before each meal. The plan of study was to give alternate patients either constantly A66 or constantly B66 for six weeks, then to change to the other tablet for six weeks. Finally, the patients were to receive for an additional six weeks the tablet they had started with. In this manner each patient could serve as her own control. However, within a few weeks it was apparent that the studies could not be followed as planned. It was readily noted by both patients and investigators that tablet A66 was the active drug and B66 the placebo. Many patients would not cooperate in taking the placebo when they were coming to the clinic for help in weight reduction. As a result, the period of observation for patients on tablet B66 was shorter, and a few patients did not receive B66 at all.

The patients were seen at two-week intervals, and at every visit they were weighed, had blood pressures and pulse rate determined and were interviewed by one of the investigators. Complete blood cell counts and urinalyses were done before and during therapy on all patients.

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RESULTS

The average period of individual patient observation was 11.5 weeks, with a range of 4 to 21 weeks. The study comprised a total of 565 patient weeks.

Weight Changes

1. Thirty-nine patients (80 per cent) showed loss of weight while taking phenmetrazine. Ten patients (20 per cent) did not lose weight, and a few gained weight while taking the drug.

2. The 49 patients received phenmetrazine for a total of 420 patient weeks. The average weight loss per week during administration was 0.82 pound (the average included the gains by some patients).

3. Thirty-three patients received the placebo for a total of 145 patient weeks and showed an average weight gain of 0.44 pound per week during this period (Table 1).

4. Thirty-three patients received the placebo and phenmetrazine alternately. The results in this group demonstrated the statistical significance of the weight-losing effect of phenmetrazine (Table 2).

Persistence of Continuous Weight Loss

During administration of phenmetrazine, the mean weight loss per week in 33 patients studied ten weeks or less was 0.77 pound. In sixteen patients studied for 11 to 18 weeks the mean weight loss was 0.88 pound per week during administration of phenmetrazine (Table 3). This difference is not significant, and the results suggest that there is no tolerance to the effect of the drug.

Relation of Age to Weight Loss

Twenty-five patients aged 45 years or less showed an average weight loss of 1.1 pounds per week during a mean study period of 9.7 weeks of treatment with phenmetrazine. Twenty-four patients over 45 years of age showed an average weight loss of 0.42 pound per week during a mean study period of 7.4 weeks for this group (Table 4).

Side Effects

No serious side effects, allergic or toxic reactions were noted. No changes were noted in the urine or in the leukocyte content of hemoglobin level of the blood before and during therapy. Significant elevation of blood pressure or pulse rate was not observed, even in patients who had moderate hypertension. Occasional subjective complaints were noted in ten patients. They consisted of one case of nausea, one of gaseousness, two of nervousness, three of insomnia and three of metallic taste. Thus, the overall incidence of side effects was 20 per cent, and these were not serious enough to warrant discontinuation of the drug except in one case because of nervousness. It should be noted that the average dose of phenmetrazine used in this study was 75 mg. per day, which is greater than the amounts reported in most of the other series and may account for the rather high incidence of minor unpleasant reactions observed. Also, it is apparent that even with the higher dosage employed, no greater weight loss was obtained. The side effects were easily controlled by decreasing the dose and/or altering the time of administration. The subjectivity of a number of side effects is emphasized by the finding that 10 per cent of the patients given the placebo noted some of these as well. On the whole only the occurrence of a metallic taste and insomnia appeared of any consequence.

TABLE 1.—*Weight Changes in 49 Patients*

	Tablet	
	Phenmetrazine	Placebo
Number of patients	49	33
Total number of patient weeks	420	145
Average number of weeks/patient	8.6	4.4
Range of weeks of administration	4 to 18	2 to 17
Mean change in weight/patient week	—0.82 lb.	+0.44 lb.

TABLE 2.—*Weight Changes in Patient Receiving Both Phenmetrazine and Placebo*

	Tablet	
	Phenmetrazine	Placebo
Number of patients	33	33
Total number of patient weeks	313	133
Average number of weeks/patient	9.7	4.4
Range of weeks of administration	4 to 18	2 to 17
Mean change in weight/patient week	—0.64 lb.	+0.44 lb.
p value	<.001*	<.001*

*Less than 1:1000 chance of the difference being due to chance alone.

TABLE 3.—*Response to Phenmetrazine in Terms of Duration of Administration*

	Period of Rx with Phenmetrazine	
	1 to 10 Weeks	11 to 18 Weeks
Number of patients	33	16
Average number of weeks/patient	6.2	13.5
Mean weight loss/week	0.77 lbs.	0.88 lbs.
p value	>0.1*	>0.1*

*Greater than 1:10 chance of the difference being due to chance alone.

TABLE 4.—*Results in Patients in Different Age Groups During Administration of Phenmetrazine*

	Age Group	
	Under 45	Over 45
Number of patients	25	24
Average number of weeks/patient	9.7	7.4
Mean weight loss/week	1.1 lb.	0.42 lb.
p value	.015*	0.15*

*Less than 1:60 chance of the difference being due to chance alone.

DISCUSSION

To test the validity of the observed differences in weight change during administration of phenmetrazine (a reduction of 0.82 pound per week) and the placebo (an increase of 0.44 pound per week), the results in the 33 patients in the series who received both the drug and the placebo alternately, and therefore served as their own controls, were subjected to statistical analysis. The p value for this group was less than 0.001, a probability of less than one in 1000 that the results were due to chance (Table 2). The weight loss observed with phenmetrazine was less than other investigators have reported. It should be emphasized that previous studies included specific dietary restriction, which was not the case in this series and probably accounts for the differences in weight loss obtained. The lack of dietary control is a realistic approach to the usual situation in which the patient does not continue to follow a strict and rigid diet.

Most patients immediately noted the anoretic activity of phenmetrazine. In fact, the pronounced difference in anoretic activity between phenmetrazine and the placebo made it impossible to carry out the experiment as planned, since the patients were reluctant to continue taking the placebo. Another action of phenmetrazine which many patients commented upon was that they were satiated more easily, even when there was little reduction in appetite before meals.

It has been noted previously by other investigators[1] that most regimens that include anoretic agents are effective the first month or two of therapy but that the efficacy of these regimens drops sharply after this period. Such was not the case with phenmetrazine (Table 3).

Ten patients, or 20 per cent of this series, did not lose weight while taking phenmetrazine. The reason is not known but certainly the phenomenon was not unexpected. In general, however, elderly patients did not respond as well as the younger subjects, and seven of the ten patients who did not lose weight while taking phenmetrazine were over 45 years old (Table 4). The lesser loss of weight in the older age group is in keeping with the general experience that it is harder to obtain weight reduction in older subjects. This can not be related to the anoretic factor but must be attributed to other factors, for the most part unknown, that influence body weight changes with increasing age.

Since there were no serious side effects, notably allergic and cardiovascular symptoms, phenmetrazine appears to be a safe and valuable adjunct to the dietary management of obesity.

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